American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

MEDICAL PASSPORT

Name _____ Address _____

Date of birth _____ Place of birth _____

ROUTINE (Basic) IMMUNIZATION SCHEDULE

Consult your physician. The following are suggested practices for immunization against five serious diseases to which one may be exposed before, during and after the school years.

AGE and ADMINISTRATION

DURING FIRST YEAR OF LIFE

Any time after one to two months. First polio injection. Second injection four to six weeks later. Third injection seven months after second injection. (Consult your physician for schedule if oral polio vaccine is used).

At two months. First of a series of DTP vaccine to protect against diphtheria, tetanus and pertussis (whooping cough). A second injection and a third injection are given at monthly intervals. If the quadruple vaccine (DTPP), which is now available, is used, three injections are given at monthly intervals, and an additional injection six to twelve months after the third injection. (Consult your physician for schedule if oral polio vaccine is used).

At four to six months. Smallpox vaccination.

AFTER FIRST YEAR OF LIFE

At 16 to 18 months and at four years of age. "Booster" injection of DTP or quadruple vaccine (DTPP).

At five to six years, or on entering school. Smallpox revaccination. Polio "booster" injection.

After six years. "Booster" injection of diphtheria-tetanus (DT) vaccine every four to five years. Polio "booster" injection every two to three years.

DURING LATER YEARS **and throughout life.**

"Booster" inoculations or oral doses (if used) are essential for continuing maximum protection. Your physician will indicate the most suitable schedule and time period.

IMMUNIZATION RECORD

DISEASE	INJECTION	DATE COMPLETED	PRODUCT USED
Diphtheria			
Tetanus	First		
Pertussis (Whooping Cough)	Second		
DTP, a triple vaccine, combining all three, is used.	Third		
	Booster		
Poliomyelitis			
A quadruple (DTPP) vaccine, consisting of DTP and Polio Vaccines, may be used for injection.	First		
	Second		
	Third		
Indicate if oral polio vaccine is given.	Booster		
Smallpox	First (vaccination)		
	Second (revaccination)		
	Booster		
Other Diseases			
Indicate other immunizations.			

(See article, page 267)

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American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

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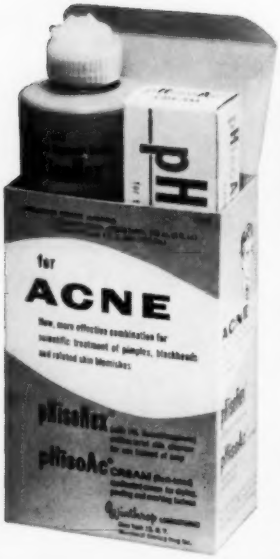

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Vol. 133 JULY 1961 No. 7

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E D I T O R I A L

PACKAGE INSERTS FOR PRESCRIPTION PRODUCTS

THE regulations issued by the Food and Drug Administration which would require that complete information concerning a given drug be inserted in the original package as distributed in professional channels is fundamentally sound. While a number of alternative proposals have been made for getting the essential information with respect to prescription drugs in the hands of pharmacists and physicians, none of these seems likely to accomplish what is the obvious intent of the Food and Drug Administration and the need for full and complete information available when and where needed by every member of the health team. The alleged prohibitive cost of such a program is not a convincing argument—not, at least, to this writer—in view of the rather extensive budget which already is devoted to distributing information about such drugs by other means. Here, we pause long enough to state that we are not opposed to medical and pharmaceutical advertising since this is a part of our distributive and informational system, and an essential part. As we see it, package inserts and the advertising of pharmaceuticals will complement and supplement one another rather than simply duplicate effort and expense.

There is no question but that a package insert in each and every package distributed is the most direct and certain means of getting this information where it is needed. This method has been used by some companies for a long time and with considerable success. From our own experience, we know how simple a matter it is to refer to such a source when some obscure point concerning dosage or contraindications is needed. While the argument may be advanced that this information is usually in the hands of the pharmacist rather than the physician, this is somewhat academic since it is the role of the pharmacist to provide the physician with just this sort of information

either verbally or, if the physician wishes, by means of a package insert delivered to him. It also means that full and complete information on prescription products is as close as the nearest pharmacy and can be obtained by the simple expedient of a telephone call with the pharmacist only too happy to be of service. Physicians will, of course, continue to have the other usual reference sources to which they are accustomed so that package inserts will not eliminate all other sources of information.

The proposals which have been made by several groups to prepare official drug brochures for distribution to members of the medical and pharmaceutical professions would, if adopted, fail to accomplish the intent of the Food and Drug Administration. Physicians are notoriously careless in their filing of such information and many pharmacists, we feel, are guilty of the same error. There is, furthermore, a long series of weaknesses in any such plan. First, how could such brochures be kept up to date and could those sending out replacement literature be sure that the physician or pharmacist would remove the old copy and replace it with the new? A second and very major problem not fully appreciated by those who have offered their services to distribute such brochures is the wording which would be used. It seems almost certain that, if any responsible group such as the American Medical Association or the United States Pharmacopeia were to engage in such a distributive mechanism, some conflict of philosophy would arise on how the wording in a given instance should be presented. It surely is inconceivable that either of these groups would be willing to accept verbatim, copy as prepared by the manufacturer and then give it the authoritative status which the U. S. P. or the A. M. A. conveys. Using the package insert approach, the wording is solely the responsibility of the manufacturer with, of course, the constant surveillance of the Food and Drug Administration—which is as it should be. We can think of many other points of difficulty. What, for example, would be done to accommodate the young physician just out of medical school? Would someone deliver to him a truckload of drug brochures with the expectation that he would assemble these and put them in proper order?

While there are many services which our professional organizations and our official compendia can properly render, this distributive mechanism does not seem to be one of them. We have

given this matter considerable thought and have become more convinced than ever that the package insert idea advanced by the Food and Drug Administration is the most direct and practical solution possible. We are also of the opinion that the Food and Drug Administration is on absolutely sound ground in issuing such a regulation in the interest of public health and safety. Its adoption and implementation cannot help but improve the practice of medicine and pharmacy and make our complex task somewhat more easy to accomplish.

L. F. Tice

TO BE OR NOT TO BE—PROFESSIONAL *

By Glenn Sonnedecker **

TODAY it seems everyone claims to be either "scientific" or "professional." If they can borrow occupational prestige with a long pedigree behind it, so much the better. Of course, you can quickly get into an argument about which profession is most ancient. For example, three men were discussing this point the other day. A surgeon offered this claim: "The Bible says that Eve was made by carving a rib out of Adam. I guess that makes mine the oldest profession." An engineer said: "Not at all. An engineering job came before that. In six days the Earth was created out of chaos—and that was really an engineer's job." A politician spoke up. "Ah, yes," said the politician, "but who created the chaos?"

Most of us, in pharmacy, seem rather confident, too, that ours must be the oldest of professions. (But about the "chaos" in pharmacy—no one, in pharmacy or out, accepts any responsibility for it.) This afternoon I hope to add not one whit of chaos, among the students of this College. That's my minimum goal! On the positive side, I hope we can come to a broader view of what it means to be "professional." Perhaps we can become more clearly aware of the inner structure of the process called professionalization, which is important. It is important because you soon will be caught up in this process personally; and how you react to it has important implications for you, for the profession itself, and ultimately for the public.

Origin of "Professions"

The question of whether or not pharmacy is an "ancient and honorable profession," as reputed need not long detain us. But we should stop and look at it long enough to see that pharmacy is more "honorable" than it is "ancient"; that it was old as a function before it was young as a profession.

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* An invitation lecture first published in *The Third Annual Lecture Series in the Pharmaceutical Sciences* (University of Texas College of Pharmacy, Austin, 1960).

** Professor (history of pharmacy), University of Wisconsin; Director, American Institute of the History of Pharmacy, Madison 6, Wisconsin.

I dare say we place no particular value upon pushing pharmacy's origin back beyond the "surgery" of carving a rib out of Adam, or beyond the "engineering" operation of the Creation! It does seem worth remarking, however, that we find pharmaceutical service emerging wherever civilization arises, for the reason that the services of your occupation stand among the most basic needs of mankind. Yet, as we look back across the ancient world we see no professionalized pharmacist. You will recall that in ancient Egypt and Babylonia we see, however dimly, pharmaceutical service combined with priestly functions, often with medicine as well. In the Greco-Roman world, pharmacy and medicine separated from the clergy, but remained joined together as a craft of health services. There was not even a term for profession as distinct from craft or technic, much less a separate profession specifically devoted to pharmacy.

The pharmacist, as a separate practitioner with recognized responsibilities to the public, becomes noticeable on the historical stage during the remarkable flowering of the medieval Arab world, sometime after the middle of the eighth century when drug therapy had become less modest and the forms of administration more elaborate.

In the West, we trace our professional lineage more directly to the late medieval cities of Europe, especially in Italy, where pharmacy took an independent place as part of a general trend based upon urbanization, upon the rise of middle class occupations among artisans no longer bound to manorial estates, and their organization into guild-like associations. At about the same time, occupations that had been carried on within the learned world of the medieval clergy became secularized. These occupational changes in the social structure were well under way in the eleventh century. From the thirteenth century in the West (notably 1240), we date legal recognition and regulation of pharmacy as an occupation separated from medicine as a matter of principle.

Out of this milieu grew the professional occupations as we now understand them. It should be recognized that the separation of practitioners of pharmacy, or even their organization into guilds, represents mainly a prerequisite to professionalization; its fulfillment came more slowly.

Since the eighteenth century a growing group of occupations has surged forward to lay claim to professional status. Thus the traditional triumvirate of the clergy, law, and medicine no longer

more or less monopolizes recognition as learned professions. Pharmacists have not been last in staking their claim. But here we are not so much interested in validating a label. We are mainly concerned with reviewing what complex of characteristics growing out of this occupational development, determines whether we are to be—or not to be—recognized as professional.

The Concept of Profession

If we ask, "What does it mean to be a 'profession'?", we probably would hear in this room many different definitions. Perhaps not one of them would be wholly wrong. If we look to the dictionaries, we find that their definitions do not entirely agree or discriminate. They do more or less agree that a profession involves a specialized, intellectual learning, which is used to render a particular service by guiding or advising others, or by practicing an art.

Even that idea, if you fit it upon a series of examples, will not distinguish professions from non-professions in a way that will bring common agreement. I agree with what Carr-Saunders says in a book on "The Professions," which remains the best discussion of its kind in English. Pointing out that there is no single test or touchstone for professionalism, he says: "It is not merely that any dividing line must be arbitrary. It is that the drawing of a line, which, though arbitrary is clear, presents great difficulties if it is not impossible. Nevertheless the term profession . . . clearly stands for something. That something is a complex of characteristics" (1).

The ensuing discussion by Carr-Saunders probably formed the basis for the more formalized construction used by Thorner in considering one aspect of pharmacy (2).

I share most of Urdang's reservations about some of Thorner's assumptions (3), but his basic guideposts to professionalization provide a framework so useful that I adopted it in discussing the subject before the First Middle East Pharmaceutical Congress in Lebanon (4); and it is from the same vantage point that I present it here today.

Five Forces of Professionalization

There are particularly five essentials or criteria that may give us a more discriminating pattern or evaluation of professional status: "(1) A relatively specific, socially necessary function upon the regular

performance of which the practitioner depends for his livelihood and social status; (II) A special technique, competence in which is demanded, resting upon; (III) A body of knowledge embracing generalized principles, the mastery of which requires theoretic study; (IV) A traditional and generally accepted ethic subordinating its adherents' immediate private interests to the most effective performance of the function; and (V) A formal association fostering the ethic and improvement of performance."

I should like to use these five points as hooks upon which to hang further comment, rather than use much of the remaining time to defend their validity. Naturally, amendments and additions could be discussed profitably.

Definitions have a static quality that tempts us to gloss over the *dynamic* quality of occupations. Imagine these five essentials as kinetic pressures giving thrust to would-be professions—not as static characteristics that we have or have not for all time to come.

Think of various occupations scattered along a continuum between two poles. For convenience, we may call the extreme opposites pure Professionalism on the one side and pure Commercialism on the other. The occupation entirely conforming to either of these ideal types of course may never be found. In concept, we put profession and commerce poles apart. But we all know that in practice they intertwine. Any sociologic study of the practice of pharmacy, for example, would have to take into account the precariousness of maintaining professional status in a milieu infused with "little business," subject to pressures and changes located in so-called "big business." Other occupations, too, are subject to cross pressures. Throughout the decades, each occupation moves erratically, slow or fast, first toward one pole then the other. What moves them? Each occupation is being pushed—buffeted, if you will—by pressures proportionate to the *combined intensity* of the professional essentials or qualities that we mentioned.

The direction of movement depends on the total kinetic energy from a balanced constellation of these forces. There is no single force —no magical touchstone, which editorial writers sometimes see or seek—that will transform pharmacy into the paragon of professions. When we develop all the essentials vigorously, an occupation moves rather steadily toward the professional ideal. But, in another circumstance, the positive pressure of, say, a well-developed and widely-

held knowledge and technique may be overcome by the counter-force of a disintegrating ethical standard. Then the occupation shifts back toward the commercial pole.

This becoming and not-becoming of professions can be observed, in the long view of history, even though it cannot be readily measured. Since the seventeenth century, the scientific revolution, the development of learned societies, and the appearance of a specialized periodical literature, all played their part in the emergence of modern professions, but at various times in different places.

Keeping in mind our conceptual image of professionalization as an ongoing process, let us now look back briefly at each of the five essentials, which collectively give the professions much of their character and status.

I

First, we expect to find "a relatively specific, socially necessary function . . ."; that pharmaceutical service fulfills such function in society seems self-evident. You see it in the groping toward pharmaceutical aid for the afflicted in primitive cultures. You see it begin to take more specific form in the relatively complex cultures of antiquity. However necessary the function, it alone contributes little toward professional standing, although the idea does promptly clarify the status of such figures as the so-called "professional athlete" or the "professional prostitute."

This first criterion becomes more significant when we note that upon his socially necessary function "the practitioner depends for his livelihood and social status." We noted that the independent practice of pharmacy rests upon a service that has high social utility; but unfortunately the *quantitative* demand for this service is not comparable to its *qualitative* value. Recognizing this circumstance led many European countries to provide or permit unusual restrictions on the number and location of pharmacies. In that way the average pharmacist can depend *primarily* upon his specialized function for his livelihood and social status. The Anglo-Saxon countries, on the other hand, decided in effect that such a restriction on individual opportunity and liberty is too high a price to pay. In these countries, the pharmacist has greater difficulty maintaining high professional status. This cannot be explained wholly by weakness in this first essential, but it illuminates an important point and problem.

Probably most American pharmacists do not aspire to a formal limitation system, because of overriding social convictions. But they are united with pharmacists elsewhere in one desire: that their central traditional function, dispensing practice, should remain within the orbit of the traditional practice of pharmacy. If this ambition has one eye on prospective financial income, the other eye is on the "psychic income" derived from a vigorous professional function. As we all know both from history and the current American circumstance, the scope of dispensing practice may atrophy by a migration of part of this function to medicine on the one side, or to unqualified personnel such as grocers on the other.

In pharmacy's relation to medicine, it remains professionally desirable—and not unreasonable—to expect the physician to accept a clear separation of the practice of pharmacy from medicine, except under defined special circumstances, just as the pharmacist assumes a firm obligation not to diagnose and prescribe, except when qualified medical service clearly is not available. The effect of the industrial revolution in pharmacy may encourage the physician, especially in private practice, to dispense certain pre-fabricated drugs from the office. At the same time, readily available service from a pharmacy is expected for all drugs that are difficult to store, to prepare, to dispense, infrequently used, or expensive to buy. If such a subdivision of function occurs—what seems to the pharmacist an unreasonable division—it becomes more difficult to maintain proper and economical service in public pharmacies.

It is always tempting to identify public interest with one's private interest; yet, a number of countries offer historical precedents for firmly separating pharmaceutical practice from medical practice, which seems in the common interest and helps pharmaceutical service to function at a quantitative level adequate to sustain a desirable level of professionalization.

On the other side of pharmacy stands the question of curbing the eagerness of unqualified personnel to dispense medicaments for self-medication. This question intertwines pharmacy's history in various countries since the Middle Ages. Here, we are more narrowly concerned with whether this type of dispensing adds to, or detracts from, the professional function and stature of the pharmacist. Certainly there remains some place for self-medication even under the most advanced socio-economic conditions and systems of medical care.

Yet, if not in accord with modern medical science, the dispensing of self-medication easily can detract from the pharmacist's professional status. Whether or not it is desirable, both professionally and socially, for these medicaments to be dispensed through the pharmacy depends ultimately upon our willingness to accept a full professional responsibility, which goes beyond the avoidance of prescribing.

This responsibility demands that the pharmacist dissociate himself completely from any misleading representation of drug products to the laity, from whatever source it comes. We all know that the acceptability and meaning of a medicament does not derive, finally, from its scientific formulation or its elegance. Essentially, the meaning lies in how it has been represented; what people believe it is and believe it will do. It deserves steadfast effort by our organizations and our schools to assure that all practitioners can intelligently safeguard the public from pharmaceutical products that may be misused or useless, and guide the unwary to qualified medical attention. If we follow this concept of responsibility to its logical conclusion, we reach the antithesis of "self-service." It implies that the pharmacist himself—and not an assistant—would dispense all drugs. If our dispensing always goes hand in hand with the social responsibility implied by the word profession, we can be certain that it will strengthen the professional function and tend to broaden the legal prerogatives of pharmacy.

Finally, we recognize that social currents of our time may reshape professional function within pharmacy itself. Here are just three examples:

(a) The industrial revolution in pharmacy, coupled with intricate advances in pharmaceutical science, has shifted technical operations from the small pharmacy to the large industrial laboratory. Self-delusion that minimizes the discomfort of change should not obscure the significant implications of this shift. It asks for imaginative application of knowledge by teachers and practitioners alike if the functions of retail pharmacy are to become professionally more robust.

(b) We have seen in other countries that the advent of systems of medical care involving health insurance may shift either the locus or focus of pharmaceutical services. This involves questions beyond the economic relation between patient and practitioner. It asks for earnest effort in all health services to maintain their professional

standards and personalized quality, their professional freedom and integrity, and their general availability through all qualified practitioners.

(c) The trend toward supplying more and more medical care through hospitals, clinics, and group medical practice may well also bring a shift in pharmaceutical practice. This development, underpinned by the advancing specialization and technology of medicine, enlarges the professional role of the pharmacist through institutional practice, even though it might have disturbing long-range implications for professional function as a means of livelihood in public pharmacies.

The three examples just mentioned are trends carried upon international currents affected but not originated by conditions peculiarly American, and they may alter the familiar structure of pharmacy at times and places not of our own choosing. New structures need not dispossess pharmacists of their home among the professions. But whether old patterns should be adapted to new conditions of practice, or new conditions should be pressed into old patterns, poses vital questions for all who value their professional heritage.

II-III

Pharmacy must adapt to the needs of our time, without losing either its individuality or its heritage. Education fosters this adaptability in the professional sphere as it does in the cultural sphere. Indeed, we note that education is the force behind the second and third essentials in the process of professionalization. The second has been referred to as "a special technique, competence in which is demanded." This in turn rests upon the third essential, "a body of knowledge embracing generalized principles, the mastery of which requires theoretic study."

It commands our special attention at this juncture in pharmacy's history that "technique" means not only, nor even first at all, manual technique. Intellectual operations, manual skills, *and* a particular set of attitudes are fused to form the technique needed to fulfill professional function (5).

Notice that the second essential of a profession also specifies that competence in the technique is not merely expected, it is "demanded." This demand is met by public certification, often through

a state examination. Licensing systems may also be applied to trades or businesses but they usually do not certify technical ability and intellectual competence, instead providing mainly assurance of integrity or the collection of special taxes.

The third essential, theoretic knowledge and understanding, must underpin the technique of every modern occupation that hopes, first, to achieve professional maturity and hopes, finally, to avoid professional senility. We see here a highly characteristic difference between professions and trades.

The need for thorough theoretic study seems self-evident among teachers of pharmacy. Sometimes, among some students and practitioners, it seems equally self-evident that a good practical education suffices for the average pharmacy. Yet, a teacher fulfills his own professional obligation only if he prepares students to seek the *best* positions in pharmacy for which their diploma will make them eligible. Likewise, a teacher prepares his students not alone for pharmacy of today, much less a former day; he tries to lay a basis for practicing pharmacy effectively a quarter of a century from now, when his students will reach their professional prime. The only hope of achieving that goal, since teachers are not prophets, hinges upon a sound theoretic background that may permit the alert graduate to change and grow with changing times.

IV

A decade ago the American Council on Education published the results of a "Pharmaceutical Survey" that was one of the most revealing studies ever made of a nation's pharmacy. The director of the survey sharpened American awareness that professionalization is not a simple correlate of scientific knowledge when he reached this conclusion: "the outstanding factor determining the future of the profession of pharmacy is fundamentally moral in nature" (6). He stressed the importance of the profession containing a high proportion of members "who are ever sharply jealous of the high reputation of the profession and who, by energetic cooperation, are determined ever to protect that reputation."

This calls attention to the importance of the fourth force of professionalization: "a traditional and generally accepted ethic subordinating its adherents' immediate private interests to the most effective performance of the function." I wonder if American pharmacy,

including its educational system, has done all that can or should be done to make us zealous to protect the reputation of pharmacy as a profession and to understand all that implies in practice?

However far governmental regulation of pharmacy may reach, room remains for a set of moral expectations and injunctions in some form—for an institutionalized action pattern that makes it normal for the pharmacist to accept social responsibilities going beyond legal compulsion. The spiritual spark of this self-imposed discipline kindles professional vigor and protects professional freedom.

"Traditional ethic" has a tradition of an existence and acceptance. I suggest that it does not imply an unchanging, merely traditional content. Although basic principles remain stable, their application must be fitted to highly particular circumstances. Thus, if a profession's ethic is to be influential in practice—and not merely admired for its lofty but elastic abstractions—then the approved action patterns had best reflect concretely the current ethical issues. In so doing, we shall want to differentiate between principles of professional etiquette, which help assure smooth and orderly relations in the professions, and principles of professional ethics, which truly touch moral or social issues affecting the patient's interests and welfare.

These questions have little more than a formal significance, however, unless a systematic and dedicated effort makes the code of ethics a living force in the professionalizing process. That is, there must be not only an ethic but a "generally accepted ethic subordinating its adherents' immediate private interests to the most effective performance of the function."

V

This brings us to the question of compliance with ethics, which is imbedded in the last essential of professionalization that we here consider, namely: "a formal association fostering the ethic and improvement of performance."

The professional society that codifies and adopts an ethical blueprint to guide its members must also decide how to make the code an organic part of the profession's life. This may be furthered by regular publication of real or hypothetic case-histories involving ethical questions, together with a discussion of the issues involved; by establishing an organizational mechanism for receiving and considering instances of alleged unethical conduct, and by providing penalties for

proved charges; and by aiding teachers and preceptors to give the ethic a central place in the educational process. Teaching the historical and social background of a profession, such as pharmacy, is also believed to help create the mental climate in which such a program can germinate and thrive.

Besides stimulating the profession's collective conscience and jealousy of its reputation, the professional association fosters other activities designed for "the improvement of performance" on the part of its constituents and, in doing so, encounters complex issues. This requires steadfastness of purpose coupled with a clear understanding of essentials. But the professional association also requires the active support and cooperation of each one who wants to live *in* a profession, and not merely live *off it*. Indeed, I should think it difficult for any occupation to keep moving in a professional direction without a group-consciousness that keeps at least a majority of its members joined in cooperative effort. Unless I am mistaken, this asks for more effective organizational support from you—from your generation of American pharmacy, and the next—than we have had in the past.

Conclusion and Outlook

So we see a complex of forces at play in pharmacy and other occupations, moving them ceaselessly back and forth along the continuum between ideal professionalism and ideal commercialism. There is no single force, no publicity agent, no white coat or mannerism, no magic formula, which alone gives an occupation the professional status its members seek. If we are to have the abiding satisfactions—the "psychic income"—as well as the money income that derive from a professionally vigorous life work, then we must keep before us a sophisticated concept of what history asks from us in return.

Sometimes we feel caught in social currents beyond control, that spin us away from our life's objectives. Yet, whether we are to be, or not to be, professional finds an answer largely within ourselves. Professional thrust derives from the individuals, cooperating individuals, of which every profession wholly consists. In a health field, such as pharmacy, concern with professional stature carries beyond a fascination with prestige and social status; for, here, a lack of professional stature can have implications for the public welfare and, ultimately, even for the survival of an occupation in its traditional sense.

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* This book discusses individual professions of Great Britain and then analyzes the structuring of professions in general.

** This is the best single source of comparative factual information on the American professions.

THE BIOLOGICAL ACTIVITY OF ORALLY ADMINISTERED DESICCATED THYROID *

By Gerhard Levy and Franklyn G. Knox

A number of reports have appeared in recent years concerning variations in the biological activity of desiccated thyroid and the apparent inadequacy of the U. S. P. assay for this substance. Jackson (1) has stated that "some thyroid preparations, even though fresh, are unreliable and of little value." Sturnick and Lesses (2) have reported that "within U. S. P. specifications, thyroid gland preparations vary in physiological activity." Kupperman (3) states that thyroid extracts having the same iodine content need not necessarily have the same physiologic activity and that, consequently, "an unusual degree of variability may be noted in a patient's response to thyroid extracts made in different commercial houses." Wayne (4) also has commented on the unreliability of thyroid tablets. Apparently, thyroid tablets have been found to vary in potency not only from manufacturer to manufacturer but also from batch to batch (5). Potency differences among tablets were as great as two and a half fold (6). Stasilli and Kroc (7) have found that thyroid powder obtained from beef exhibited only about half the biologic potency of thyroid powder derived from pork, despite the fact that both preparations were equivalent in terms of the U. S. P. assay, which is based on iodine content. On the basis of some of the reports cited here, a recent editorial in a British publication (8) has stated that the time has come to "examine the need for a biological assay, and further, to decide which method of biological assay most closely replicates clinical biological activity in man."

In view of the current interest in the clinical efficacy of thyroid substance, it is timely to review the pertinent literature concerning factors which may affect the biological activity of this drug. Furthermore, the results of an investigation of thyroid activity, which was carried out in this laboratory during 1959, are reported.

* From the Biopharmaceutics Laboratory, School of Pharmacy, University of Buffalo, Buffalo 14, New York. Supported in part by a faculty research grant from the University of Buffalo.

One factor which may account for the variability in potency of thyroid may be the instability of the thyro-active components. This possibility can be ruled out apparently, since Hubata and coworkers (9) have found that thyroid lots up to 17 years of age have demonstrated complete stability when tested by both the U. S. P. chemical assay and by biological methods. These workers also cite clinical data to show that thyroid tablets retain stability on aging. Similar conclusions have been arrived at by Wermer (10) who examined 7 year old thyroglobulin.

Another cause of variation in biological activity of thyroid could be the possible inadequacy of the official assay method. The work of Stasilli and Kroc (7) and of others demonstrates conclusively that the official assay, which is based on "iodine in thyroid combination," does not adequately reflect biological activity, and requires revision.

A report by Frieden and coworkers (11) suggests another possible reason for variation in thyroid potency. These workers examined two lots of desiccated thyroid and found that these exhibited only 71 per cent and 72 per cent, respectively, of their parenteral activity, when administered orally to rats. This suggests incomplete gastrointestinal absorption of the thyro-active components of desiccated thyroid. Chapman and coworkers (12) have shown that, when drugs are only partially absorbed, their absorption is variable and irregular. Thus, it should be possible to obtain not only higher activity but greater reproducibility in biological response from thyroid administration if means can be found to assure the complete absorbability of the drug.

While it is known that the thyroid gland contains at least eight different iodinated amino acids (13), only l-thyroxine (T-4) and 3:5:3′-triiodo-l-thyronine (T-3) are biologically active (14). These compounds occur bound to protein in the form of thyroglobulin, a macromolecule with a molecular weight close to 650,000 (15). When administered orally, thyroglobulin undergoes enzymatic hydrolysis. The resulting free T-4 and T-3 are then absorbed across the gastrointestinal membranes. If enzymatic hydrolysis is incomplete, part of the thyro-active compounds will not be available for absorption, since only the free or non protein-bound thyroid hormones can pass across biological membranes (16). Likewise, if hydrolysis is complete but so slow that the thyro-active compounds may not be fully released until the drug has passed to the lower portion of the intestine, time

may be insufficient for the drugs to be absorbed before they are propelled past the absorption sites. The absorption-limiting effect of the hydrolysis process has been demonstrated recently in the case of another drug, chloramphenicol palmitate (17). In the case of iodo-proteins, the rate of enzymatic hydrolysis is much lower than that of the corresponding non-iodinated proteins (18), so that it appears entirely reasonable to assume that slow or incomplete hydrolysis and the resultant incomplete gastrointestinal absorption may be responsible for the lower biological activity of orally administered thyroid substance.

Tong and Chaikoff have recently described a method for the analysis of iodine-containing compounds in thyroid tissue (19). By means of an enzymic hydrolysis technique, they obtained a recovery of approximately 95 per cent of the thyroglobulin in the form of iodo-amino acids. Their favorable results were apparently due, to some extent at least, to a very effective pancreatic enzyme preparation (Viokase) and to the hydrolysis-enhancing effect of certain divalent cations (Mn^{++}, Mg^{++}, and Ca^{++}). The availability of the procedure described by Tong and Chaikoff suggested an experiment in which the biological activity of orally administered, *pre-hydrolyzed* thyroid substance be compared with the activity of untreated thyroid substance. Such an experiment could help to indicate the possible absorption-limiting role of gastrointestinal hydrolysis, in case the latter is slow or incomplete. At the same time, prehydrolysis of thyroid substance appeared to be promising as a means of enhancing the therapeutic efficacy of desiccated thyroid powder.

Experimental

Bioassay: The goiter-prevention assay proposed by Dempsey and Astwood (20) was used to determine the biologic activity of thyroid. Female Wistar rats weighing 150 to 200 Gm. were fed a normal diet [1] to which 0.3 per cent 2-thiouracil and an appropriate amount of thyroid were added. Addition of drug to the diet is more convenient than oral gavage and has been used successfully by Stasilli and Kroc (7) and other workers who are cited in the reference. Herrold and coworkers have employed this method for the assay of thyroid powder and have reported on its sensitivity (21). After 14 days, the animals

[1] Big Red Rat and Mouse Diet, manufactured by Co-operative G. L. F. Exchange, Inc., Canandaigua, New York.

were sacrificed, weighed, and their thyroid glands were removed and weighed to the nearest 0.1 mg. All dissections were carried out by the same individual to rule out variations due to differences in technique.

Enzymatic Hydrolysis:—One-hundred and twenty-five mg. each of desiccated thyroid powder and Viokase were added to 20 ml. of an aqueous solution containing sodium bicarbonate (0.05 M) and sodium chloride (0.11 M). The dispersion was incubated at 37° ± 0.5° in a water bath for the specified length of time. After hydrolysis, the aqueous dispersion was incorporated in the powdered diet which was then compressed into larger pieces.

Materials:—Thyroid, U. S. P. (Armour Laboratories, Kankakee, Illinois)[2] containing 0.2067 per cent iodine by U. S. P. assay (22); 2-thiouracil, (Nutritional Biochemicals Corp., Cleveland, Ohio); Viokase, (Viobin Corp., Monticello, Illinois), described as activated whole raw pancreas which has been desiccated and defatted, and as equivalent to 4 times U. S. P. pancreatin (23).

Results and Discussion

The results of the experiments to be discussed are summarized in Table I. Since certain environmental factors such as temperature, season, age, humidity, stress, and nutrition can affect the experimental results (20, 24, 25), the experiments were designed so that comparisons involved only simultaneously performed experiments, rather than comparison of results obtained at different times.

Experiment A shows the thyroid weights of animals on a normal diet and those on a goiterogenic diet. The latter developed marked goiters. The gland weights of both groups are of the same order as those reported by other workers using this general method (26).

Experiment B demonstrates the sensitivity of the goiter-prevention assay in our hands. The two dosage levels were chosen so that they may reflect the possible differences in potency which could be present in subsequent experiments: the lower dose was 70 per cent of the higher dose just as the reported oral activity of thyroid powder was about 70 per cent of the same dose when administered paren-

[2] Kindly supplied by Dr. T. Douglass, Quality Control Department, Armour Laboratories.

TABLE 1

EFFECT OF ENZYMATIC DIGESTION ON ACTIVITY OF DESICCATED THYROID

Experiment	*Treatment* [1]	*No. of Animals*	*Average Thyroid Weights* [2]	*Standard Deviation*	*Significance of Differences*
A	none	12	10.9	3.2	$P < .001$
	300 mg. thiouracil	12	42.8	8.8	
B	300 mg. thiouracil, 12.5 mg. thyroid	12	35.8	7.0	$P < .001$
	300 mg. thiouracil, 17.85 mg. thyroid	12	19.7	5.6	
C	300 mg. thiouracil, 12.5 mg. thyroid, 2 Gm. pancreatic enzymes	12	26.3	7.5	n.s.
	300 mg. thiouracil, 12.5 mg. thyroid	12	30.2	4.7	
D	300 mg. thiouracil, 12.5 mg. thyroid incubated 10 hrs. with pancreatic enzymes	12	27.5	6.0	n.s.
	300 mg. thiouracil, 12.5 mg. thyroid	11 [3]	27.2	5.7	
E	300 mg. thiouracil, 12.5 mg. thyroid incubated 24 hrs. with pancreatic enzymes and 0.05 M. Mn++.	12	26.8	4.5	$P < .05$
	300 mg. thiouracil, 12.5 mg. thyroid	12	30.8	4.6	

[1] Addition to 100 Gm. of normal diet.

[2] mg. per 100 Gm. body weight.

[3] Data from 12th animal unavailable due to accidental cutting of gland.

terally (11). The results show that the method is sufficiently sensitive for the purpose of the present investigation.

Experiment C was designed to determine the possible *in vivo* hydrolysis-enhancing effect of added pancreatic enzymes. The enzyme preparation used is not vitiated by gastric secretions and may, therefore, be administered as part of the diet. A slightly higher activity of desiccated thyroid was exhibited in the group which received the diet containing pancreatic enzymes. However, the difference between these results and the results obtained from the control group were not statistically significant.

Experiment D was designed to indicate the effect of relatively mild prior enzymatic hydrolysis on the biological activity of thyroid powder. Tong and Chaikoff (19) obtained maximum yields of thyroxine after 8-24 hours of digestion. Accordingly, the enzymatic digestion period for this experiment was chosen to be 10 hours. No enhancement of activity was apparent.

A more vigorous hydrolytic procedure was used for Experiment E. The digestion time was lengthened to 24 hours and 0.05 M. Mn^{++} was added to the hydrolysis medium in view of the hydrolysis-enhancing effect of this cation (19). A small, but statistically significant enhancement of biological activity by prior hydrolysis was apparent. By reference to the results of experiment B, it can be seen that the increase in activity was no greater than 5 to 10 per cent.

The results of the described experiments suggest that slow or incomplete gastrointestinal hydrolysis is only a minor factor in the possible incomplete gastrointestinal absorption of the thyro-active components of desiccated thyroid. However, such a conclusion applies only to the conditions of the goiter prevention test in rats, where the powdered drug is incorporated in the diet and is ingested over the entire day. In clinical use, the drug is administered under less ideal conditions. It is usually given in one to three doses a day in the form of compressed tablets. The tablets occasionally may disintegrate very slowly, be impacted in gastrointestinal contents, or be propelled rapidly past the absorption sites. Under such circumstances, the *in vivo* hydrolysis of thyroglobulin would be incomplete and the physiological availability of the drug could be diminished markedly. Thus, it is possible that pre-hydrolysis of desiccated thyroid may increase the efficacy of this drug to a greater extent with respect to clinical use than is shown by these experiments on rats.

It must be recognized that failure of the tablets to disintegrate promptly into small particles could reduce absorption and biological activity. For example, it has been shown with chloramphenicol palmitate (17) that large particle size results in lower absorption due to decreased hydrolysis rate which, in the case of solids, is a function of surface area, among others. The U. S. P. tablet disintegration time limit for thyroid tablets appears much too long under the circumstances, especially since *in vivo* disintegration of compressed tablets as judged by X-ray takes considerably longer than under the conditions of the *in vitro* U. S. P. test.* An examination of commercial thyroid tablet preparations known to have been stored on pharmacy shelves for several years revealed that some tablets exhibited disintegration times in excess of one hour. Such tablets, while fully potent on the basis of a bioassay (for which the tablets would be finely crushed prior to administration to the test animals), could be clinically unsatisfactory.

Since slow or incomplete *in vivo* hydrolysis of the thyroglobulin appears to contribute very little to the lower activity of orally administered desiccated thyroid when given experimentally to rats, it appears that an inherently poor absorption of T-4, T-3, or of both these hormones from the gastrointestinal tract may be responsible. On the basis of data derived from a number of publications by different workers, it is feasible to examine this possibility on a semi-quantitative basis.

It has been recognized that T-4 is poorly and incompletely absorbed from the gastrointestinal tract (27, 28). Blackburn and Keating (29) found T-4 administered intravenously to human patients approximately twice as effective as when given orally in the control of myxedema. Similar results were reported by Tomich and Woollett (30) and by Frieden and coworkers (11) with respect to T-4 activity in rats. Kroc and coworkers (31) reported that orally administered T-4 had 34 per cent the activity of the drug when given subcutaneously, and Gross and Pitt-Rivers (32) reported that oral T-4 exhibited 39 per cent the parenteral activity of the drug. While it must be recognized that the degree of absorption may differ to some extent with dose and mode of administration, and that the precision of the quantitative determinations is not particularly high, it is reasonable to conclude that in most instances only about 40 to 50 per

* Levy, G., Unpublished Data.

cent of the drug is absorbed by both humans and rats after oral administration.

A different picture is obtained in the case of T-3. This drug is considered to be readily absorbed from the gastrointestinal tract of man (33). Selenkow and Asper (34) observed that T-3 produces the same response in the treatment of myxedema when administered by mouth as by the intravenous route, and concluded that the drug is apparently absorbed almost completely from the gastrointestinal tract. Similarly, Blackburn and Keating (29) have found that T-3 is only "slightly more effective" intravenously than orally. In rats, the drug is equally effective when given by oral or parenteral route, according to Tomich and Woollett (30). Gross and Pitt-Rivers (32) have determined and expressed oral activity of T-3 in rats more quantitatively. These workers reported an activity of 86 per cent compared with an equal parenteral dose.

T-3 is considerably more potent than T-4. Estimates of relative potency differ depending on the assay method, and also vary from laboratory to laboratory using a given assay method. Currently available data have been summarized by Pitt-Rivers and Tata (35). According to their tabulation, T-3 is 2.8 to 5.4 times as potent as T-4 in man, and 2.5 to 6.0 times as potent as T-4 in rats, on the basis of goiter prevention activity. Thus, the ratio of activities is about equal in man and in rats and is, on the average, 4-1 (T-3:T-4). It is of interest that the two hormones also differ qualitatively: T-3 has a considerably shorter latent period of action in man as well as a biological half-life about one-third that of thyroxine (36). The latter appears to be related to the relative affinity of these two compounds to a serum protein (37, 38).

If the extent of gastrointestinal absorption of T-3 and T-4, their relative biological activity, and the concentration ratio in which they occur in desiccated thyroid is known, it is possible to estimate the potency difference between orally and parenterally administered desiccated thyroid powder. Unfortunately, very little information is available about the concentration ratio of T-3 to T-4 in thyroid glands, probably due to the pronounced experimental difficulties associated with such determinations. Mandl and Block (39) recently have reported new methods for the determination of iodo-amino acids in iodo-proteins and found a T-4:T-3 ratio of 7:4 in a commercial thyroglobulin (Proloid) quite similar to that in desiccated thyroid.

More recent data obtained by these workers from crude thyroglobulin seem to show a ratio averaging closer to 3:1 (40). Stolc and Podoba (41) reported data yielding a ratio of 2:1, but these workers used rat thyroids which need not necessarily reflect the ratio of the two hormones as found in the glands of other species. An indirect estimate of the T-4:T-3 concentration ratio in desiccated thyroid U. S. P. can be obtained from the data of Frieden and Winzler (26). These workers reported that desiccated thyroid is about 4 times as potent as dl-thyroxine by the goiter-prevention method, using doses equivalent in "thyroxine iodine" as determined by Blau's method. It is now known that the butyl alcohol extraction described by Blau yields not only T-4, but also T-3 (31). On the basis of the biological activity ratios l-thyroxine (T-4) : dl-thyroxine = 2:1, T-4:T-3 = 1:4; and desiccated thyroid: dl-thyroxine = 4:1, one may calculate a T-4:T-3 concentration ratio of 2:1. Thus,

if 100 parts of dl-thyroxine have an activity of 1
100 parts of T-4 " " " " 2
and 100 parts of T-3 " " " " 8
(since T-3 is 4 times as potent as T-4),

then, assuming a 2:1 concentration ratio (T-4:T-3) in desiccated thyroid,

$$\frac{67}{100} \times 2 = 1.3 \text{ potency units}$$

$$\frac{33}{100} \times 8 = 2.7 \text{ potency units}$$

Total for 100 parts of mixture having a ratio T-4:T-3 = 2:1 = 4.0 potency units

which, of course, is the activity ratio shown experimentally by Frieden and Winzler (26). Having available now quantitative estimates of the T-4:T-3 activity ratio, the concentration ratio of these two substances in desiccated thyroid, and their degree of absorption, it is possible to calculate the activity of orally administered desiccated thyroid as compared with an equal but parenterally administered dose of the drug.

In case of parenteral administration:

	Concentration Ratio		*Activity Ratio*		*Activity Units*
T-4:	2	×	1	=	2
T-3:	1	×	4	=	4
				Total Activity:	6

In case of oral administration:

	Concentration Ratio		*Activity Ratio*		*Degree of Absorption*[3]	*Activity Units*
T-4:	2	×	1	×	.39	.8
T-3:	1	×	4	×	.86	3.4
					Total Activity:	4.2

Thus, orally administered desiccated thyroid would have $\frac{4.2}{6.0} \times 100$, or 70 per cent, of the parenteral activity of the drug. This is very similar to the experimental results of Frieden and coworkers (11), who found that two desiccated thyroid preparations exhibited 71 and 72 per cent, respectively, of their parenteral activity when administered orally. The close agreement of the theoretical and experimental data is an additional, though indirect, indication that the *in vivo* hydrolysis is not a major factor in the incomplete gastrointestinal absorption of orally administered thyroid by rats. The preceding calculations can, at best, only be considered semi-quantitative and await the availability of more precise data for a rigorous verification. However, these calculations, considered together with the experimental results, are compatible with the assumption that the lower activity of orally administered desiccated thyroid in rats is due mainly to the incomplete absorption of thyroxine, but that slow or incomplete *in vivo* hydrolysis also may have a small but significant effect on the biological activity of the drug. Since the conditions under which the drug is administered to humans are less conducive to efficient absorption than the conditions of the animal test, it is conceivable that prior hydrolysis may enhance the efficacy of desiccated thyroid in therapeutics to a greater extent than is reflected by the animal data.

[3] Based on the data reported by Gross and Pitt-Rivers (*32*).

Summary

Factors which may influence the biological activity of orally administered desiccated thyroid are reviewed. The possible absorption-limiting effect of slow or incomplete gastrointestinal hydrolysis of the drug has been investigated. On the basis of the experimental results and of semi-quantitative estimations using data from the literature, it may be concluded that the lower biological activity of orally administered thyroid in rats, when compared with the activity of parenterally administered drug, is due primarily to the incomplete absorption of thyroxine, one of the thyro-active components of desiccated thyroid. It was possible to enhance the activity of thyroid slightly by enzymatic hydrolysis of the drug prior to its oral administration to rats. In view of the less favorable conditions for absorption associated with the clinical use of the drug, it is possible that prior hydrolysis may result in greater enhancement of the biological activity of desiccated thyroid when used in therapeutics.

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"MEDICAL PASSPORT"

By Louis Gershenfeld *

DO you remember accurately *when* and the *kind of injections* for immunization you and your children were given?

Do you remember accurately the communicable diseases you and your children have had in the past?

The possession of accurate up-to-date records or certificates of all the immunizations (injections, vaccinations, and/or oral doses) received and when they were given will save inconvenient calls, worry, time, and money. This together with a log of infectious diseases you and your dear ones have had and their outcome may on some occasions even obviate treatment by the attending physician, to be given during illness and in the prevention of certain diseases, unless he is certain of your past record.

In our country, the military immunization program, at all times, consists in the main of routine practices. The more comprehensive procedures are applied to everyone in the military services only against real hazards, when encountered in the specific areas, where the individual may be during periods of operation. Certain immunizations for special situations are practiced at infrequent occasions. They are not used routinely, and are reserved only for those exposed to unusual opportunities for infection, as when present in or departing for or traveling through areas where the specific protection is particularly indicated. Frequently, they are to meet a future rather than an existing situation. It is well to note here how records of immunizations performed during military service were kept during World War II. The completion of tetanus immunization was noted by embossing the identification tag with the numerals of the years of completion of the basic series and the booster (or stimulating) dose. Each individual immunized had his tetanus immunization record with him and, thus, available at all times. The records for all other immunizations received by each individual in the military service were treated differently. Personnel was frequently transferred to

* Director, School of Bacteriology, Philadelphia College of Pharmacy and Science.

new areas. However, the written immunization records did not follow as quickly to the respective stations and, occasionally, not at all. Accordingly, immunizations were repeated unnecessarily, with resultant inconvenience, loss of time, and unnecessary expense. This was corrected, in part, when the immunization records together with other official papers were given to each one as they were transferred. A more suitable practice was later instituted when provisions were made for each individual to have a complete copy of his own record in his possession at all times. This is as it should be for every individual, in or out of the military services.

It is important that everyone recognize that the proper preparation and maintenance of accurate records of immunization are desirable, and all must be made to understand that it is a necessity. Entirely too many immunizations have been and are being repeated unnecessarily because of the failure in having available one's complete immunization status. Such information is of considerable value to those responsible for medical care in the community, as well as to the individual concerned. The attending physician and/or those health workers authorized to conduct specific immunizations, more so than others, are in the best position to supply the patient with the necessary information, indicating the importance of keeping accurate records.

At present, accurate records of specific immunizations are available for each individual in the military services, the Peace Corps, and for the personnel in the State Department and other governmental agencies where compulsory immunizations of proven value are practiced, if they are traveling to and through areas, where the specific protection is indicated. However, we have here individuals who might be regarded as a captive group. They *must* follow orders.

Most of the immunization practices among civilians in the United States are on a voluntary basis. There are, of course, some few exceptions. Among the latter, we find that everyone (no exceptions) traveling to foreign countries *must* possess an International Certificate of Vaccination or Revaccination against smallpox. This Certificate, to be used for recording data, is supplied when one applies and receives a passport or visa. Unless the traveler has been successfully vaccinated within three years prior to entry or re-entry and has an *approved* record of this, he will not be allowed to enter or re-enter the United States. Otherwise, he will be vaccinated at the port of entry, or he will be kept in quarantine for a period of two weeks.

There are no Federal laws requiring the civilian population to be immunized against smallpox or other diseases. Most States regulate such practice, and the specific requirement varies among the many States. The more general or routine procedures are immunization practices against smallpox, diphtheria, whooping cough, tetanus and, more recently, against poliomyelitis. Even in those instances, the regulations in these States, wherever compulsory, do not usually apply to the entire population, but only to the school population and specifically to those entering public, private, or parochial schools. Usually, the school medical services (and they alone) have such records. Many of the desirable immunizations are given on a voluntary and not a compulsory basis.

The primary school is the most convenient and perhaps the most logical place for providing children with useful, up-to-date health information given, as far as possible, before they acquire incorrect or outdated notions in this respect from home or outside sources. It is desirable to have school children, especially, arrange and maintain their own immunization records, as soon as they can read and write. Such responsibility started early in life will not only supply a more accurate record, but it is bound to make them aware of the value of good health and of health knowledge in general. This special practice, offering as it does a positive, direct, and specific approach to disease prevention and control, makes them aware of the need of receiving booster (or stimulating) doses, so as to maintain a high level of immunity, serves also as a means for promoting valuable health information and for obtaining interest and cooperation in such matters during one's lifetime. It is bound to aid in making the adult of tomorrow health-conscious and strengthen the physician- and public health-patient relationship through increased public understanding of the significance of the numerous roles the attending physician and the health worker play in the lives of everyone in their respective communities and, in fact, everywhere.

So-called "immunization schedules" or "immunization certificates" are available and even supplied by some health departments. The Maryland State Department of Health issues a "Birth Registration Notice," when registering a child's birth. The back of this "official document" has imprinted thereon data concerning immunizations required for diphtheria, pertussis, poliomyelitis, smallpox, and tetanus. A leaflet developed as a joint project of the U. S. P. H. S.

and the American Academy of General Practice is for sale by the U. S. Government Printing Office, Washington 25, D. C. The immunization schedule for the five diseases previously mentioned is given and space is available to indicate when the inoculations were completed.

The writer has prepared an immunization schedule and record. Space is available to list the infectious diseases as they occur and other pertinent data, if desired. To popularize this, it has been designated as a "Medical Passport." Comprising as it does a health service project of the Philadelphia College of Pharmacy and Science, the "Medical Passport" is distributed by this institution. Single copies or a number as required for other members of your family are available on request.

Use the "Medical Passport" or keep a similar record for everyone in your family, if each is to enjoy maximum protection. It is of value to assure maximum infectious disease protection, expediting treatment during certain illnesses. It may be needed if you change physicians, move to a new school district, when entering college or places of employment or joining the armed forces, for preparing for travel in foreign countries, or if injured, or when certain epidemics prevail. Such a "Health Record" for each member of your family will actually serve as a kind of "Medical Passport," if it is kept up to date and reviewed periodically.

BOOK NOTICES AND REVIEWS

Heterocyclic Compounds, Vol. 7. Robert C. Elderfield, Editor. vii + 878 pp. John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y. 1961. Price: $37.50.

This latest volume of the well-known series includes the chemistry of polycyclic compounds containing two hetero atoms in different rings and five and six membered heterocycles containing three hetero atoms and their benzo derivatives. The material is encompassed in ten chapters which include naphthyridines, carbolines, phenanthrolines, triazoles, triazines, oxadiazoles, oxadiazines, thiadiazoles, thiadiazines, and those compounds containing two hetero-oxygen atoms in different rings.

The editor states that many problems were involved with the publication of this volume—some of the manuscripts being many years old. However, an attempt to include coverage of the English and German literature through 1959 has been made.

Due to the somewhat prohibitive cost of the book, it may be well to consider reducing the scope of future volumes so that the individual chemist may purchase those volumes of particular interest. Nevertheless, most medicinal and pharmaceutical chemists will find a wealth of information correlated in this single volume and should plan to include it in their libraries.

A. R. GENNARO

British National Formulary, 1960, Alternative Edition. British Medical Association and the Pharmaceutical Society of Great Britain. 292 pp. The Pharmaceutical Press, 17 Bloomsbury Square, London, 1960. Price: $1.75.

The *Alternative Edition* of the *British National Formulary, 1960* differs from the Standard Edition in that this book is based on a pharmacological classification. This book does not contain appendix for Equivalent Metric and Imperial Doses and Dental Practitioners' Formulary which are in the Standard Edition.

Indian Essential Oils, A Review. By A. K. Menon. Council of Scientific & Industrial Research, New Delhi, India. 89 pp. S. N. Guha Ray at Sree Saraswaty Press Ltd., 32, Acharya Profulla Chandra Road, Calcutta 9, India, 1960.

This book is divided into "Essential Oils," "Spice Oils," "Attars and Aqueous Products," "Natural Isolates," and "Aromatic Chemicals." Information such as production, commerce, botanical origin, commercial sources and uses are given. An extensive bibliography is included.

Management of Hypertensive Diseases. By Joseph C. Edwards. 439 pp. The C. V. Mosby Company, St. Louis, Mo., 1960. Price: $14.50.

This book is intended to serve as a guide to the practical management of the patient with hypertensive disease. It is written for the busy physician in practice who wants the latest information on the treatment of hypertension and guidance in selecting proper medication for a particular patient. This book will aid in a better understanding and a more logical use of the available agents in the management and control of hypertension.

The mechanism of the physiology and chemistry of the neurocirculatory system are not discussed in detail. However, a review of the experimental work and clinical studies of therapy in recent years has been added. The chapters covered in this book are: Arterial Hypertension and its Diagnosis, Heart Disease with Hypertension, Electrocardiogram in Hypertension, Natural History of Essential Hypertension, Management of the Patient with Hypertension, Special Problems in Management of the Patient with Hypertension, Hypertension Associated with Pregnancy, Special Types of Hypertension (Secondary Factor), Antihypertensive Drugs (Pharmacology and Therapy), and Etiology of Hypertension with Special Reference to Essential Hypertension.

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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